

PCT



WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



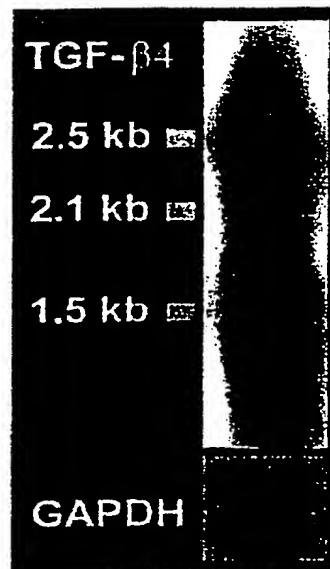
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12Q 1/00		A1	(11) International Publication Number: WO 99/55902
			(43) International Publication Date: 4 November 1999 (04.11.99)
(21) International Application Number: PCT/US99/09366 (22) International Filing Date: 29 April 1999 (29.04.99) (30) Priority Data: 60/083,418 29 April 1998 (29.04.98) US (71) Applicant (for all designated States except US): UNIVERSITY OF SOUTH FLORIDA [US/US]; 4202 Fowler Avenue, FAO 126, Tampa, FL 33620 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): TABIBZADEH, Siamak [US/US]; 71 Parkview Drive, Searingtown, NY 11507 (US). (74) Agent: KOHN, Kenneth; Kohn & Associates, Suite 410, 30500 Northwestern Highway, Farmington Hills, MI 48334 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: DIAGNOSTIC MARKERS OF HUMAN FEMALE INFERTILITY

(57) Abstract

There is provided a method for diagnosing endometrial irregularities particularly infertility by screening an endometrial sample or bodily fluid for the presence of ebaf. Also provided is a diagnostic tool for determining the presence of endometrial irregularities screens a sample for the presence of ebaf. A contraceptive containing an effective amount of ebaf and a pharmaceutically acceptable carrier is also provided. Additionally, a diagnostic kit for timing conception is provided having a screening tool for screening a sample for the presence of ebaf. Also provided is a method of treating endometrial irregularities by down-regulating the expression of ebaf.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09366

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C12Q 1/00

US CL : 435/6

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,E	US 5,916,751 A (TABIBZADEH et al) 29 June 1999, see abstract, claims and entire document.	1-40
Y	US 5,395,825 A (FEINBERG et al) 07 March 1995, see col. 3, line 56, col. 5, line 10, col. 6, lines 7-26; col. 8, lines 21-68 and claims, see entire document.	4,13-15, 27-36,40
Y	US 5,693,479 A (FEINBERG et al) 02 December 1997, see col. 3, line 56; col. 5, line 10; col. 6, lines 7-26; col. 8, lines 21-68; and claims, see entire document.	4, 13-15, 27-36, 40

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or when is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
28 AUGUST 1999

Date of mailing of the international search report

10 SEP 1999

Name and mailing address of the ISA US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer

GINNY PORTNER

Telephone No. (703) 308-0196

JOYCE BRIDGERS
PARALEGAL SPECIALIST
CHEMICAL MATRIX

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09366

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, DIALOG, ALL MEDICINE, MEDLINE

search terms: cbaf, tgfbeta4, endometri?, fertili? , infertili?

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09366

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,554,339 A (COZZETTE et al) 10 September 1996, see figure 7a and entire document.	1, 3-6, 8-13, 15, 17
X	US 5,709,837 A (MORI et al) 20 January 1998, see abstract, claims 9, 19 and entire document.	1, 3, 4, 6, 7
X	US 5,286,624 A (TERASHIMA et al) 15 February 1994, see abstract, col. 3-5, 8-9 and claims.	13, 14, 16, 18
X	US 5,420,016 A (BOGUSLASKI et al) 30 May 1995, see abstract and entire document.	1, 3, 5-7

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

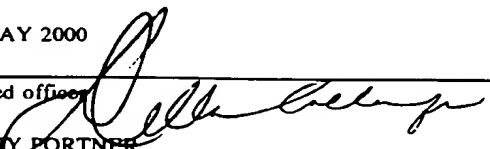
REC'D 18 JUL 2000

WIPO

PCT

Applicant's or agent's file reference 0152.00332	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/09366	International filing date (day/month/year) 29 APRIL 1999	Priority date (day/month/year) 29 APRIL 1998
International Patent Classification (IPC) or national classification and IPC IPC(6): C12Q 1/00 and US Cl.: 435/6		
Applicant UNIVERSITY OF SOUTH FLORIDA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of <u>4</u> sheets. <input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of <u>0</u> sheets.
3. This report contains indications relating to the following items: I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step or industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 15 FEBRUARY 2000	Date of completion of this report 22 MAY 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  GINNY PORTNER
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/09366

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/09366

I. Basis of the report**1. With regard to the elements of the international application:***☒ the international application as originally filed☒ the description:

pages 1-90 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:

pages 1-40 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:

pages 1-9 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:

pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig. NONE

5. ☒ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/09366

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims <u>1-40</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1-3,5-12,16-26,36-39</u>	YES
	Claims <u>4,13-15,27-35,40</u>	NO
Industrial Applicability (IA)	Claims <u>1-40</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-3, 5-12,16-26,37-39 meet the criteria set out in PCT Article 33(3), because the prior art does not teach or fairly suggest the claimed invention of diagnosing endometrial irregularities based upon the measurement of the cbaf gene and splice variants thereof.

Claims 4,13-15,27-35 and 40 lack an inventive step under PCT Article 33(3) as being obvious over Feinberg et al (US Patent 5,395,825 or 5,693,479). The references teach methods of measuring TGF4, which is also known as Ebaf, wherein the levels of expressed TGF4 are associated with competence of a conceptus toward implantation. Measurement of TGF4 levels is suggested to be in bodily fluids or cell types associated with implantation. Specific means, methods and suggested levels for measurement are taught (see col. 3, line 56; col. 5, line 10; col. 6, lines 7-26; col. 8, lines 21-68 and claims). Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to measure TGF4 levels as the prior art suggests the measurement correlates with pregnancy associated events and the person of ordinary skill in the art would be motivated to measure those indicator associated with measuring fertility for therapeutic and diagnostic purposes, specifically measuring TGF4.

Claims 1-40 meet the criteria set out under PCT Article 33(2) and 33(4).

----- NEW CITATIONS -----

NONE

PCT
INTERNET COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 December 1999 (01.12.99)	
International application No. PCT/US99/09366	Applicant's or agent's file reference 0152.00332
International filing date (day/month/year) 29 April 1999 (29.04.99)	Priority date (day/month/year) 29 April 1998 (29.04.98)
Applicant TABIBZADEH, Siamak	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
21 October 1999 (21.10.99)☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. Mafia Telephone No.: (41-22) 338.83.38
---	--